

*Original Article*

# Multicenter, Double-Blind, Randomized, Placebo-Controlled, Parallel-Group Study of the Efficacy, Safety, and Tolerability of THC:CBD Extract and THC Extract in Patients With Intractable Cancer-Related Pain

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## Abstract

**Objectives.** This study compared the efficacy of a tetrahydrocannabinol: cannabidiol (THC:CBD) extract, a nonopioid analgesic endocannabinoid system modulator, and a THC extract, with placebo, in relieving pain in patients with advanced cancer.

**Methods.** In total, 177 patients with cancer pain, who experienced inadequate analgesia despite chronic opioid dosing, entered a two-week, multicenter, double-blind, randomized, placebo-controlled, parallel-group trial. Patients were randomized to THC:CBD extract (n = 60), THC extract (n = 58), or placebo (n = 59).

**Results.** The primary analysis of change from baseline in mean pain Numerical Rating Scale (NRS) score was statistically significantly in favor of THC:CBD compared with placebo (improvement of  $-1.37$  vs.  $-0.69$ ), whereas the THC group showed a nonsignificant change ( $-1.01$  vs.  $-0.69$ ). Twice as many patients taking THC:CBD showed a reduction of more than 30% from baseline pain NRS score when compared with placebo (23 [43%] vs. 12 [21%]). The associated odds ratio was statistically significant, whereas the number of THC group responders was similar to placebo (12 [23%] vs. 12 [21%]) and did not reach statistical

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significance. There was no change from baseline in median dose of opioid background medication or mean number of doses of breakthrough medication across treatment groups. No significant group differences were found in the NRS sleep quality or nausea scores or the pain control assessment. However, the results from the European Organisation for Research and Treatment of Cancer Quality of Life Cancer Questionnaire showed a worsening in nausea and vomiting with THC:CBD compared with placebo ( $P = 0.02$ ), whereas THC had no difference ( $P = 1.0$ ). Most drug-related adverse events were mild/moderate in severity.

**Conclusion.** This study shows that THC:CBD extract is efficacious for relief of pain in patients with advanced cancer pain not fully relieved by strong opioids.

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### Key Words

Cancer, pain, tetrahydrocannabinol, cannabidiol, Sativex®

## Introduction

Cancer pain is a common problem, and 70%–90% of patients with advanced cancer experience significant pain.<sup>1</sup> Opioids remain the keystone for the treatment of moderate to severe cancer pain; however, some patients experience inadequate pain relief with opioids and standard adjuvant analgesics despite dose adjustments, and unacceptable side effects are common.<sup>2,3</sup>

Cannabis contains 60 or more cannabinoids (CBs). The main ones include delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD).<sup>4,5</sup> There is evidence that both THC and CBD show promise in relieving cancer-related pain.<sup>6,7</sup> Sativex® (THC:CBD), an endocannabinoid system modulator, is produced by GW Pharma Ltd, United Kingdom. It is derived from strains of *Cannabis sativa* L. plants developed to produce high and reproducible yields of principal CBs (THC and CBD), with minor amounts of other CBs and terpenes in a solution containing ethanol, propylene glycol, and peppermint oil flavoring.<sup>5</sup> The named CBs constitute at least 90% of the total CB content of the extracts.

CBs act primarily through specific CB receptors: CB<sub>1</sub> receptors are predominantly distributed in the central nervous system, and CB<sub>2</sub> receptors are located primarily in the periphery (including the immune system). The principal pharmacological effects of THC include analgesia, muscle relaxation, antiemesis, appetite stimulation, and psychoactivity.<sup>8</sup> CBD has shown anticonvulsant, muscle relaxant,

anxiolytic, neuroprotective, antioxidant, and antipsychotic activity, and has also been shown to reduce the anxiety and psychoactive effects of THC.<sup>9,10</sup> Preliminary tests of pharmacology and behavioral activity support the similarity of the endogenous CB anandamide to THC.<sup>11</sup> Both are partial agonists at the CB<sub>1</sub> receptor. CBD, in contrast, binds weakly to CB<sub>1</sub> and CB<sub>2</sub> but does show pharmacological potency as a neutral antagonist at each receptor,<sup>12</sup> that is, is silent at such receptors but can reverse both agonist and inverse agonist responses. CBD also has shown powerful anti-inflammatory, immunomodulatory,<sup>13</sup> and antioxidant properties in vitro.<sup>14</sup> It is a transient receptor potential vanilloid receptor 1 (TRPV1) vanilloid receptor agonist in its own right, while modulating anandamide by inhibiting both its reuptake and hydrolysis.<sup>15</sup> Additionally, CBD increases adenosine A<sub>2A</sub> receptor signaling by inhibition of the adenosine transporter.<sup>16</sup> Both THC and CBD have shown analgesic efficacy in animal models.<sup>10,17,18</sup> In this study, both a THC:CBD extract and a THC-only extract were compared against placebo to ascertain if the inclusion of CBD provided a different efficacy or safety profile.

Campbell et al.<sup>19</sup> published a literature review of nine randomized controlled trials performed using CBs (any route of administration) in patients with acute, chronic nonmalignant, or cancer pain. Five studies that were described in four reports comprised 128 patients with cancer pain.<sup>6,7,20,21</sup> All of the trials

conducted on patients with cancer pain were placebo-controlled trials. Four of the trials found CB as effective as codeine but with dose-limiting side effects. Thus, CBs have demonstrated efficacy comparable to selected opioids.

THC:CBD is the first endocannabinoid system modulator to undergo clinical development for pain. It has been approved in Canada for the relief of neuropathic pain in multiple sclerosis and persistent background cancer-related pain. The formulation is an oromucosal spray that allows flexible, individualized dosing. Patients self-titrate their overall dose and pattern of dosing according to their response to, and tolerance of, the medicine, with administration of approximately 8–12 sprays/day, that is, 22–32 mg/day THC and 20–30 mg/day CBD. This study assessed the analgesic efficacy of THC:CBD and THC extracts compared with that of placebo in the management of patients with at least moderately severe cancer-related pain despite appropriate pharmacological management.

## Methods

This two-week (two days' baseline and two weeks' treatment), multicenter, double-blind, randomized, placebo-controlled, parallel-group study evaluated the efficacy of THC:CBD extract and THC extract in the analgesic management of patients with moderate to severe cancer-related pain. There was a two-day baseline period. Adult male or female patients who had been using strong opioids for at least one week to relieve pain associated with incurable malignancy and who gave written informed consent were screened for study entry. Eligible patients recorded a pain severity score of 4 or above on a 0–10 Numerical Rating Scale (NRS) on both days of the two-day baseline period. Patients were excluded if they had cancers affecting the oral cavity; radiotherapy to the floor of the mouth; major psychiatric or cardiovascular disorders; epilepsy; renal or hepatic impairment; or if they were pregnant, lactating, or not using adequate contraception. Patients who had received therapies expected to confound the study outcome (epidural analgesia within 48 hours of screening; palliative radio-, chemo-, or hormonal therapy within two weeks of

screening; or CBs within seven days of randomization) were also excluded. Patients taking levodopa, sildenafil, or fentanyl or patients with a hypersensitivity to CBs were excluded on safety grounds. Patients completed a study diary, recording pain score three times daily and background medication and all additional breakthrough analgesia on each day during the baseline period. Patients then returned for assessment, randomization, and dose introduction to one of the three treatment arms: THC:CBD extract, THC extract, or placebo (Fig. 1) in a 1:1:1 treatment allocation ratio. Patients were reviewed after 7–10 days (Visit 2) and at the end of study (14–20 days) or withdrawal (Visit 3). During the medication dosing period, the patients continued to complete the daily study diaries with the aforementioned information and the number of doses of study medication taken. The relevant regulatory authorities and research ethics committees approved the study.

The study medication was delivered using a pump action oromucosal spray. Each 100- $\mu$ L actuation of the pump containing the THC:CBD extract delivered a dose containing 2.7 mg THC and 2.5 mg CBD. Each 100- $\mu$ L actuation of the pump containing the THC extract delivered a dose containing 2.7 mg THC, and each actuation of placebo delivered only excipients plus colorants. The maximum permitted dose of all study medication was eight actuations in any three-hour period and 48 actuations in any 24-hour period.

Patients self-titrated to their optimal dose over the seven days of Week 1, based on efficacy, tolerability, and the maximum permitted dose. Patients could increase the total number of sprays each day by a maximum of 50% until they either had satisfactory relief of their symptoms or developed unwanted effects, such as intoxication (“high”). The total number of sprays was spread over the day with a minimum of 15 minutes between any two sprays. If unwanted effects developed on a new number of sprays, the patient would not take any further sprays for three to four hours. The patient would then go back to taking their further sprays at a similar level to the previous day. Once the patient had found the maximum number of sprays per day that they tolerated well or the number that provided good symptom relief, they continued with approximately

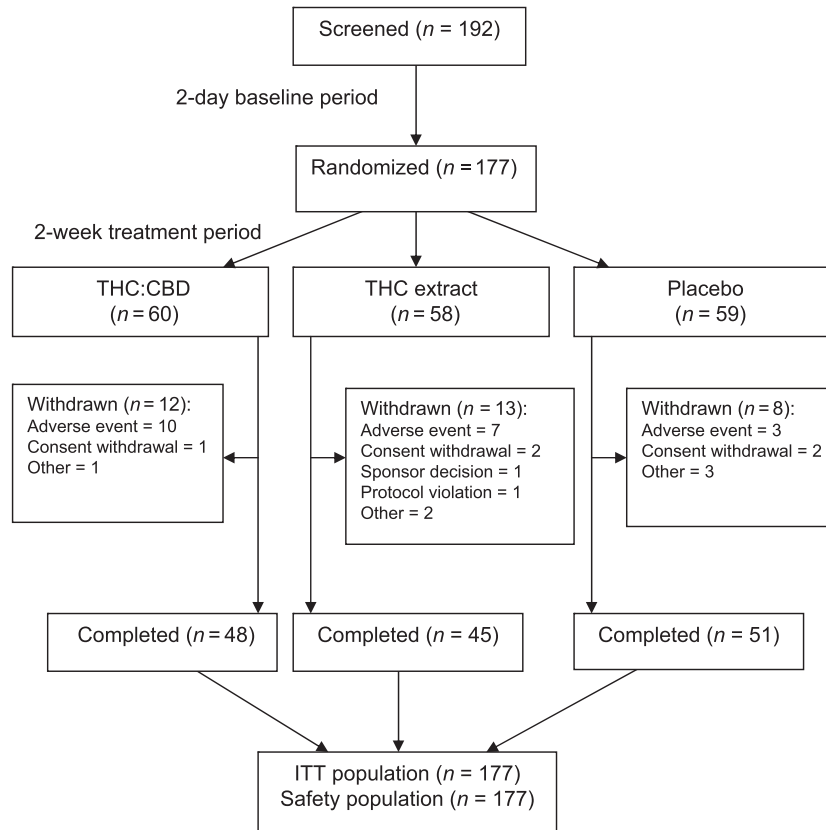


Fig. 1. Study design (Consolidated Standards of Reporting Trials [CONSORT] diagram). ITT = intent to treat.

the same number of sprays per day for the remainder of the study.

The coprimary endpoints were the change from baseline in NRS pain score and use of breakthrough analgesia. The NRS, a widely used and validated measure of pain severity, is capable of showing clinically and statistically significant changes in pain disorders.<sup>22,23</sup> The NRS question “indicate your level of pain” was answered by patients three times daily (in the morning on waking, at lunchtime, and in the evening before retiring), using the anchors 0 = no pain and 10 = very bad pain. Patients were allowed to use their breakthrough analgesia as required, and this was recorded daily in the diary. Patients maintained background medication for the duration of the study. The secondary endpoints included the use of opioid background medication, patient assessments of sleep quality, nausea, memory, concentration, and appetite over the previous 24 hours using diary NRSs. The Brief Pain Inventory-Short Form (BPI-SF) and The European Organisation for Research and

Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ-C30) Version 3 were completed by patients at Visit 1 and at the end of the study.<sup>24,25</sup> The BPI-SF consists of nine questions; eight have a single response, and Question 9 is subdivided into seven parts. The Total BPI (Questions 3–6) is the unweighted sum of the four pain scores and represents the pain intensity. The Total BPI for Question 9 is the unweighted sum of the seven assessments and represents the effect of pain. The EORTC QLQ-C30 cancer questionnaire consists of 30 questions that cover global health status, functional scales (e.g., physical functioning), and symptoms (e.g., fatigue).

Adverse events (AEs) and use of concomitant medications were reported by patients at study visits throughout the trial. Predefined categories for determining the intensity and the relationship to study medication were used. The expert clinical judgment from the investigating study physicians was used in determining intensity and causal relationship of AEs and serious AEs.

The study was powered assuming an underlying treatment difference of 1 point on an NRS and a standard deviation (SD) of 1.6 (estimated from previous studies), with 80% power and two-sided 5% significance.<sup>26,27</sup> After allowing for 15% dropouts, 58 subjects per group were required. For the two coprimary efficacy variables (NRS pain score and use of breakthrough medication), the Hochberg<sup>28</sup> method was used to test the global hypothesis for a treatment effect on pain. The null hypothesis was to be rejected if either coprimary variable produced two-sided  $P \leq 0.025$  or both produced  $P \leq 0.05$ . The daily pain NRS score was the mean of the three daily assessments. The change in mean NRS pain score from baseline (all days in run-in period) to the end of treatment (last three days on treatment) was analyzed using analysis of covariance (ANCOVA), with baseline pain as a covariate and grouped study center and treatment as factors.<sup>29,30</sup> The proportions of responders (patients with  $\geq 30\%$  improvement from baseline to end of study NRS pain score) were compared between treatments. Use of breakthrough medication (number of days of

use during last three days on treatment) was analyzed using logistic regression with a cumulative logit model. In addition, the change from baseline in mean number of doses of escape medication was analyzed using ANCOVA.

## Results

A total of 192 patients were screened over 25 months, leading to 177 patients randomized to treatment (Fig. 1) at 28 European centers. The mean (SD) duration of cancer in these patients was 3.5 years (2.8 [3.27], 3.2 [4.27], and 4.5 [5.25] years, respectively, in the THC:CBD, THC, and placebo groups, respectively). The mean age, gender distribution, previous cannabis use, primary disease sites, and pain classification were similar among the three treatment groups (Table 1). The most common type of cancer pain was of mixed pathophysiology, followed by bone and neuropathic pain (Table 1). At baseline, the mean daily dose of opioid background medication in the whole study population was 271 mg of oral morphine equivalents. The median oral

Table 1  
Patient Demographics

| Demographics                               | THC:CBD        | THC            | Placebo        | Total          |
|--|----------------|----------------|----------------|----------------|
| Gender, <i>n</i> (%)                       |                |                |                |                |
| Male                                       | 33 (55)        | 30 (52)        | 32 (54)        | 95 (54)        |
| Female                                     | 27 (45)        | 28 (48)        | 27 (46)        | 82 (46)        |
| Ethnic origin, <i>n</i> (%)                |                |                |                |                |
| Caucasian                                  | 59 (98)        | 57 (98)        | 58 (98)        | 174 (98)       |
| Other                                      | 1 (2)          | 1 (2)          | 1 (2)          | 3 (2)          |
| Previous cannabis use, <i>n</i> (%)        | 6 (10)         | 6 (10)         | 7 (12)         | 19 (11)        |
| Age (years), mean (SD)                     | 59.4 (12.1)    | 61.3 (12.5)    | 60.1 (12.3)    | 60.2 (12.3)    |
| Duration of cancer (years), mean (SD)      | 2.8 (3.3)      | 3.2 (4.3)      | 4.5 (5.3)      | 3.5 (4.4)      |
| BMI, mean (SD)                             | 23.1 (4.2)     | 23.5 (5.2)     | 24.1 (4.3)     | 23.6 (4.6)     |
| Primary cancer sites, <i>n</i> (%)         |                |                |                |                |
| Breast                                     | 12 (20)        | 8 (14)         | 9 (15)         | 29 (16)        |
| Prostate                                   | 6 (10)         | 8 (14)         | 10 (17)        | 24 (14)        |
| Lung                                       | 7 (12)         | 9 (16)         | 4 (7)          | 20 (11)        |
| Pain classification, <i>n</i> (%)          |                |                |                |                |
| Mixed                                      | 31 (52)        | 28 (48)        | 30 (51)        | 89 (50)        |
| Bone                                       | 16 (27)        | 24 (41)        | 25 (42)        | 65 (37)        |
| Neuropathic                                | 11 (18)        | 11 (19)        | 17 (29)        | 39 (22)        |
| Visceral                                   | 14 (23)        | 12 (21)        | 11 (19)        | 37 (21)        |
| Somatic/incident                           | 7 (11)         | 5 (9)          | 6 (10)         | 18 (10)        |
| Baseline morphine equivalents <sup>a</sup> |                |                |                |                |
| Median (mg)                                | 80.0           | 120.0          | 120.0          | 120.0          |
| Range                                      | 0–6,000        | 0–1,280        | 0–6,000        | 0–6,000        |
| Mean (+SD)                                 | 258.4 (789.47) | 188.2 (234.49) | 367.0 (886.38) | 271.2 (698.98) |
| 1st–3rd quartile                           | 30–180         | 50–213         | 40–240         | 40–240         |

BMI = body mass index.

<sup>a</sup>Oral morphine equivalence data are sourced from Refs. 43–45.

Table 2  
Change in Dose of Opioid Background Medication (Oral Morphine Equivalents) and Strong Opioid Breakthrough Medication

| Opioid characteristics   | THC:CBD       | THC           | Placebo        | All             |
|--|---------------|---------------|----------------|-----------------|
| Opioid background medication: change from baseline to last 3 days on study medication (patients with data available, excluding 3 patients receiving intrathecal opioids) |               |               |                |                 |
| <i>n</i> (% ITT population)  | 60 (100)      | 58 (100)      | 58 (98)        | 176 (99)        |
| Median   | 0.0           | 0.0           | 0.0            | 0.0             |
| Range  | −627 to 300   | −27 to 1,088  | −1,200 to 400  | −1,200 to 1,088 |
| Mean (±SD)   | −3.5 (108.44) | 26.9 (152.00) | −41.4 (201.27) | −6.4 (160.60)   |
| Q1, Q3   | 0, 0          | 0, 0          | 0, 0           | 0, 0            |
| Opioid background medication: categorized change from baseline in oral morphine equivalents per day  |               |               |                |                 |
| Increase, <i>n</i> (%)   | 6 (12)        | 6 (12)        | 4 (7)          | 16 (10)         |
| No change, <i>n</i> (%)  | 41 (79)       | 40 (77)       | 43 (80)        | 124 (78)        |
| Decrease, <i>n</i> (%)   | 5 (10)        | 6 (12)        | 7 (13)         | 18 (11)         |
| Strong opioid breakthrough medication: categorized change from baseline in number of doses taken   |               |               |                |                 |
| <i>N</i> (% ITT population)  | 22 (37)       | 18 (31)       | 19 (32)        | 59 (33)         |
| Increase, <i>n</i> (%)   | 2 (9)         | 4 (22)        | 7 (37)         | 13 (22)         |
| No change, <i>n</i> (%)  | 12 (56)       | 10 (56)       | 12 (63)        | 34 (58)         |
| Decrease, <i>n</i> (%)   | 8 (36)        | 4 (22)        | 0              | 12 (20)         |

ITT = intent to treat; SD = standard deviation.

morphine equivalent dose was slightly lower in the THC:CBD group at baseline compared with the THC and placebo groups (Table 2). For all three treatment groups, the predominant primary reason for discontinuing the study was AEs (Fig. 1).

The mean (SD) number of sprays taken per day, which had stabilized by the end of the first week (Days 1–7) ending the titration phase, were THC:CBD extract, 8.75 (5.14); THC extract, 8.34 (5.17); and placebo, 9.61 (4.67) (Fig. 2). Overall, for the entire treatment period, the mean (SD) number of sprays used daily in the placebo group (10.88 [5.81]) was higher than those in the THC:CBD (9.26 [5.53]) and THC groups (8.47 [5.46]).

### Efficacy

The mean (SD) baseline NRS pain scores were similar among treatment groups and within grouped centers (THC:CBD extract = 5.68 [1.24], range = 2.33–8.25; THC extract = 5.77 [1.33], range = 2.87–9.33; placebo = 6.05 [1.32], range = 3.5–9.56). The adjusted mean reduction in NRS (ANCOVA) for THC:CBD, THC, and placebo groups at the end of the treatment were −1.37, −1.01, and −0.69 points, respectively.<sup>31</sup> The adjusted mean treatment difference from placebo was statistically significant for a reduction in pain with the THC:CBD extract (0.67 points,  $P=0.014$ ) but not the THC extract (0.32 points,  $P=0.245$ ). The ANCOVA did not have normally distributed residuals, but

the nonparametric analysis gave a similar result. The median changes from baseline for THC:CBD, THC, and placebo groups were −1.36, −1.00, and −0.60, respectively. The median difference from placebo was statistically significant for a reduction in pain, which was in favor of THC:CBD extract (0.55 points,  $P=0.024$ ) but not for the THC extract (0.24 points,  $P=0.204$ ). Sensitivity analyses of the change from baseline in the mean NRS scores concurred with the primary analysis.

In chronic pain trials, it is recommended that the percentages of patients obtaining reductions in pain intensity of at least 30% on a pain NRS (responders) should be documented.<sup>32</sup> A reduction in pain NRS of approximately 30% is considered to represent a clinically important difference.<sup>23</sup> In the intent-to-treat responder analysis, approximately twice as many patients in the THC:CBD group had a reduction from baseline NRS of at least 30% compared with the placebo and THC groups (THC:CBD = 23 [43%] vs. THC = 12 [23%], placebo = 12 [21%]). The odds ratio for the comparison of responders between THC:CBD and placebo was 2.81 (95% confidence interval [CI] = 1.22, 6.50;  $P=0.006$ ), and between THC and placebo was 1.10 (95% CI = 0.44, 2.73;  $P=0.28$ ) (Fig. 3).

The number of days on which any breakthrough medication was used was similar among all treatment groups, with no significant differences observed in this clinical trial of brief duration (THC:CBD vs. placebo:

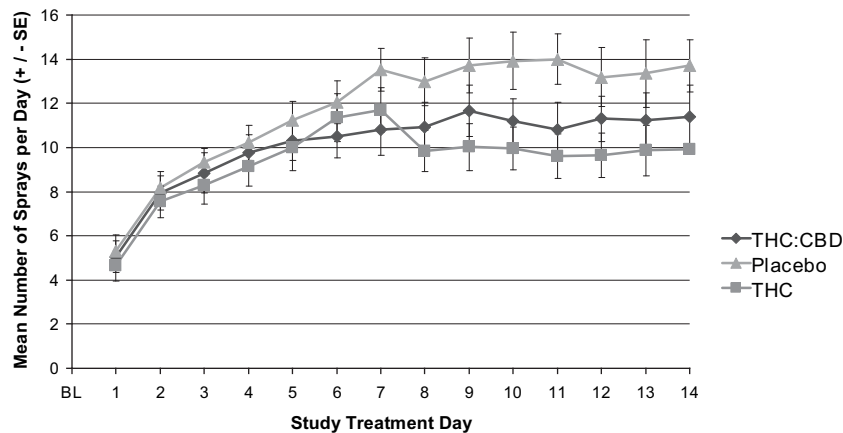


Fig. 2. Exposure to study medication—mean number of sprays per day. SE = standard error.

$P=0.70$ ). There was a reduction observed in the mean number of daily doses of all breakthrough medication (THC:CBD extract =  $-0.19$ ; THC extract =  $-0.14$ ; placebo =  $-0.15$ ) by the end of the study period, but the difference in change from baseline between treatment groups was not statistically significant. More specifically, there was no change from baseline to the last three days of treatment in the median oral morphine equivalent dose of opioid background medications in 124 (78%) patients for whom the data were available. Doses were increased for 16 patients (10%) and reduced for 18 (11%); these changes were evenly distributed across the three treatment groups (Table 2). During the baseline period or last three days on treatment, strong opioid breakthrough medication was recorded by 59 patients (33%); of these, 34 (58%) showed no change in the number of

doses taken when comparing baseline with last three days of treatment, 13 (22%) increased the number of doses, and 12 (20%) reduced the number of doses taken. A greater proportion of patients in the THC:CBD group (eight patients) reduced breakthrough doses; conversely, the highest proportion of increases in dose was in the placebo group (seven patients), which was statistically significantly greater than those in the THC:CBD group ( $P=0.004$ ).

Most of the NRS diary symptom scores and investigator-assessed pain control showed no significant treatment differences between the three groups (Table 3). A statistically significant difference in improvement with placebo was observed in the diary NRS concentration and memory scores, whereas the placebo group showed a mean improvement from baseline in concentration score ( $-0.35$ ) and the THC:CBD group showed a deterioration ( $0.33$ ,  $P=0.02$ ), as did the THC group ( $0.29$ ,  $P=0.03$ ). The memory score showed no change in the placebo group ( $0.01$ ), but a deterioration in the THC:CBD group ( $0.63$ ,  $P=0.045$ ) and in the THC group ( $0.66$ ,  $P=0.053$ ). Similarly, the appetite diary NRS score showed a mean improvement from baseline in the placebo group, and there was a slight reduction in appetite score in both THC:CBD and THC groups ( $-0.59$  vs.  $0.24$ ,  $P=0.016$ ; and  $-0.59$  vs.  $0.06$ ,  $P=0.056$ , respectively) (Table 3).

The QLQ-C30 showed, as expected, few differences among treatment groups in the two-week follow-up. Of the 16 items assessed, the only statistically significant observations were

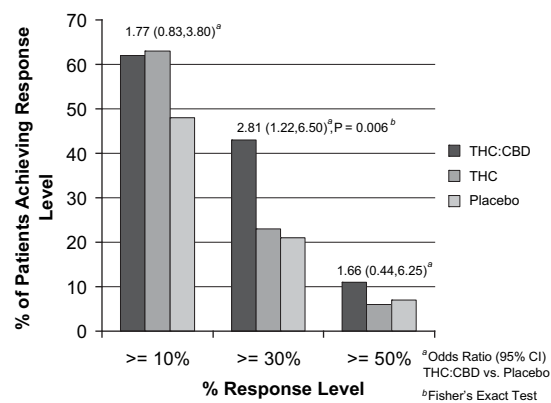


Fig. 3. Pain 0–10 Numerical Rating Scale scores: responder analysis (ITT analysis). <sup>a</sup>Odds ratio (95% CI) THC:CBD vs. placebo; <sup>b</sup>Fisher's exact test.

Table 3  
 Primary and Secondary Endpoints Showing Baseline Score, Change from Baseline, Treatment Difference, and Statistical Significance of the Difference in Change From Baseline for CBD:THC, THC, and Placebo

| Endpoint  | Treatment Group | Baseline | Change From Baseline | Comparison With Placebo |                                   |
|---|-----------------|----------|----------------------|-------------------------|-----------------------------------|
|   |                 |          |                      | Treatment Difference    | Statistical Significance, P Value |
| Mean pain severity NRS score (coprimary)                | THC:CBD         | 5.68     | -1.37                | -0.67 <sup>a</sup>      | 0.014                             |
|   | THC             | 5.77     | -1.01                | -0.32 <sup>a</sup>      | 0.245                             |
|   | Placebo         | 6.05     | -0.67                | —                       | —                                 |
| Breakthrough medication: no. of days used (coprimary)   | THC:CBD         | —        | —                    | OR = 0.96 <sup>a</sup>  | 0.697                             |
|   | THC             | —        | —                    | OR = 1.20 <sup>b</sup>  | 0.555                             |
|   | Placebo         | —        | —                    | —                       | —                                 |
| Breakthrough medication: mean daily dose                | THC:CBD         | 0.91     | -0.19                | -0.04 <sup>a</sup>      | 0.688                             |
|   | THC             | 1.10     | -0.14                | 0.01 <sup>b</sup>       | 0.899                             |
|   | Placebo         | 0.80     | -0.15                | —                       | —                                 |
| Mean sleep quality NRS score                            | THC:CBD         | 4.33     | -0.57                | -0.31 <sup>a</sup>      | 0.346                             |
|   | THC             | 4.46     | -0.24                | 0.02 <sup>b</sup>       | 0.95                              |
|   | Placebo         | 4.17     | -0.26                | —                       | —                                 |
| Mean nausea NRS score                                   | THC:CBD         | 2.44     | 0.26                 | 0.49 <sup>b</sup>       | 0.110                             |
|   | THC             | 2.04     | 0.24                 | 0.46 <sup>b</sup>       | 0.126                             |
|   | Placebo         | 1.98     | -0.22                | —                       | —                                 |
| Mean memory NRS score                                   | THC:CBD         | 3.02     | 0.63                 | 0.65 <sup>b</sup>       | 0.045                             |
|   | THC             | 2.98     | 0.66                 | 0.62 <sup>b</sup>       | 0.053                             |
|   | Placebo         | 2.90     | 0.01                 | —                       | —                                 |
| Mean concentration NRS score                            | THC:CBD         | 3.59     | 0.33                 | 0.68 <sup>b</sup>       | 0.021                             |
|   | THC             | 3.53     | 0.29                 | 0.64 <sup>b</sup>       | 0.028                             |
|   | Placebo         | 3.37     | -0.35                | —                       | —                                 |
| Mean appetite NRS score                                 | THC:CBD         | 4.83     | 0.24                 | 0.83 <sup>b</sup>       | 0.016                             |
|   | THC             | 4.58     | 0.06                 | 0.66 <sup>b</sup>       | 0.056                             |
|   | Placebo         | 4.98     | -0.59                | —                       | —                                 |
| Pain control assessment proportion with pain controlled | THC:CBD         | 50%      | 1%                   | OR = 1.70               | 0.488                             |
|   | THC             | 54%      | -2%                  | OR = 1.76               | 0.400                             |
|   | Placebo         | 36%      | -4%                  | —                       | —                                 |
| Mean BPI-SF total pain in last 24 hours                 | THC:CBD         | 20.88    | -0.17                | -1.04 <sup>a</sup>      | 0.619                             |
|   | THC             | 21.29    | -3.20                | -4.07 <sup>a</sup>      | 0.048                             |
|   | Placebo         | 23.48    | 0.87                 | —                       | —                                 |
| Mean BPI-SF total interference by pain in last 24 hours | THC:CBD         | 46.63    | -3.53                | -4.84 <sup>a</sup>      | 0.325                             |
|   | THC             | 39.39    | -4.50                | -5.81 <sup>a</sup>      | 0.275                             |
|   | Placebo         | 51.05    | 1.31                 | —                       | —                                 |
| Mean QLQ-C30 global health status                       | THC:CBD         | 29.74    | 7.23                 | 2.47 <sup>a</sup>       | 0.443                             |
|   | THC             | 27.05    | 5.60                 | 0.84 <sup>a</sup>       | 0.793                             |
|   | Placebo         | 25.29    | 4.77                 | —                       | —                                 |
| Mean QLQ-C30 physical functioning                       | THC:CBD         | 40.34    | -6.92                | -4.23 <sup>b</sup>      | 0.108                             |
|   | THC             | 35.56    | -3.94                | -1.25 <sup>b</sup>      | 0.631                             |
|   | Placebo         | 34.14    | -2.69                | —                       | —                                 |
| Mean QLQ-C30 role functioning                           | THC:CBD         | 29.02    | -0.02                | 3.31 <sup>a</sup>       | 0.415                             |
|   | THC             | 28.65    | -0.12                | 3.21 <sup>a</sup>       | 0.434                             |
|   | Placebo         | 25.00    | -3.33                | —                       | —                                 |
| Mean QLQ-C30 emotional functioning                      | THC:CBD         | 24.44    | 7.70                 | 6.73 <sup>a</sup>       | 0.084                             |
|   | THC             | 22.41    | 6.19                 | 5.22 <sup>a</sup>       | 0.174                             |
|   | Placebo         | 25.37    | 0.98                 | —                       | —                                 |
| Mean QLQ-C30 cognitive functioning                      | THC:CBD         | 50.57    | -5.33                | -9.01 <sup>b</sup>      | 0.022                             |
|   | THC             | 56.32    | -6.77                | -10.46 <sup>b</sup>     | 0.008                             |
|   | Placebo         | 50.85    | 3.68                 | —                       | —                                 |
| Mean QLQ-C30 social functioning                         | THC:CBD         | 29.02    | 3.19                 | 1.61 <sup>a</sup>       | 0.679                             |
|   | THC             | 29.89    | 9.66                 | 8.08 <sup>a</sup>       | 0.038                             |
|   | Placebo         | 25.71    | 1.58                 | —                       | —                                 |
| Mean QLQ-C30 fatigue                                    | THC:CBD         | 71.55    | -3.92                | -2.71 <sup>a</sup>      | 0.422                             |
|   | THC             | 70.69    | -1.36                | -0.15 <sup>a</sup>      | 0.965                             |
|   | Placebo         | 64.56    | -1.21                | —                       | —                                 |
| Mean QLQ-C30 nausea and vomiting                        | THC:CBD         | 25.57    | 5.13                 | 8.56 <sup>b</sup>       | 0.020                             |
|   | THC             | 22.13    | -3.41                | 0.02 <sup>b</sup>       | 0.997                             |
|   | Placebo         | 21.75    | -3.43                | —                       | —                                 |
| Mean QLQ-C30 pain                                       | THC:CBD         | 83.62    | -15.64               | -6.34 <sup>a</sup>      | 0.107                             |
|   | THC             | 79.60    | -15.71               | -6.41 <sup>a</sup>      | 0.103                             |
|   | Placebo         | 81.64    | -9.30                | —                       | —                                 |

(Continued)

Table 3  
Continued

| Endpoint                            | Treatment Group | Baseline | Change From Baseline | Comparison With Placebo |  |
|-------------------------------------|-----------------|----------|----------------------|-------------------------|--|
|                                     |                 |          |                      | Treatment Difference    | Statistical Significance, <i>P</i> Value |
| Mean QLQ-C30 dyspnea                | THC:CBD         | 40.23    | -1.09                | -0.80 <sup>a</sup>      | 0.846                                    |
|                                     | THC             | 43.27    | 4.21                 | 4.49 <sup>b</sup>       | 0.282                                    |
|                                     | Placebo         | 34.46    | -0.28                | —                       | —  |
| Mean QLQ-C30 insomnia               | THC:CBD         | 52.30    | -6.15                | -1.05 <sup>a</sup>      | 0.833                                    |
|                                     | THC             | 51.15    | -0.41                | 4.69 <sup>b</sup>       | 0.347                                    |
|                                     | Placebo         | 51.41    | -5.10                | —                       | —  |
| Mean QLQ-C30 appetite loss          | THC:CBD         | 60.34    | -3.69                | -0.88 <sup>a</sup>      | 0.857                                    |
|                                     | THC             | 54.60    | -1.19                | 1.62 <sup>b</sup>       | 0.743                                    |
|                                     | Placebo         | 59.32    | -2.81                | —                       | —  |
| Mean QLQ-C30 constipation           | THC:CBD         | 50.00    | -5.74                | -7.97 <sup>a</sup>      | 0.077                                    |
|                                     | THC             | 33.33    | -3.11                | -5.35 <sup>a</sup>      | 0.233                                    |
|                                     | Placebo         | 40.68    | 2.23                 | —                       | —  |
| Mean QLQ-C30 diarrhea               | THC:CBD         | 13.22    | -2.15                | -1.57 <sup>a</sup>      | 0.615                                    |
|                                     | THC             | 8.62     | 0.56                 | 1.15 <sup>b</sup>       | 0.713                                    |
|                                     | Placebo         | 12.99    | -0.58                | —                       | —  |
| Mean QLQ-C30 financial difficulties | THC:CBD         | 58.05    | -5.58                | -1.70 <sup>a</sup>      | 0.714                                    |
|                                     | THC             | 59.20    | -8.93                | -5.05 <sup>a</sup>      | 0.276                                    |
|                                     | Placebo         | 57.06    | -3.88                | —                       | —  |

<sup>a</sup>In favor of active treatment.<sup>b</sup>In favor of placebo.

reductions in cognitive function score when compared with placebo (THC:CBD extract = -5.33 vs. 3.68,  $P=0.02$ ; THC extract = -6.77 vs. 3.68,  $P=0.01$ ) and a worsening of “nausea and vomiting” score in the THC:CBD, although not in the THC only group, when compared with placebo (THC:CBD = 5.13 vs. -3.43,  $P=0.02$ ; THC = -3.41 vs. -3.43;  $P=1.0$ ). A trend toward improvement was seen in both active treatment groups in the QLQ-C30 pain assessment score (THC:CBD extract = -15.64 vs. -9.30,  $P=0.11$ ; THC extract = -15.71 vs. -9.30,  $P=0.10$ ) and in the constipation score (THC:CBD = -5.74 vs. 2.23,  $P=0.08$ ; THC = -3.11 vs. 2.23,  $P=0.23$ ).

### Safety and Tolerability

The active compounds were generally well tolerated, and no safety concerns were identified during this study. Treatment-related AEs were reported by 106 (60%) patients. Common treatment-related AEs (three or more patients) were similar to those seen in other THC:CBD clinical trials: somnolence, dizziness, and nausea, mostly of mild or moderate severity (Table 4).<sup>26,27,33-38</sup> The incidence of death in this advanced cancer population was similar across treatment groups (eight THC:CBD, eight THC, seven placebo), and

all were considered because of progression of underlying disease. None of the cases from the 10 patients who reported nonfatal serious AEs (SAEs) raised any concerns regarding the safety of CBs. The nonfatal SAEs of urinary retention, tumor-related pain, worsened nausea, weakness, tumor hemorrhage, and somnolence were experienced by five patients in THC:CBD group, all of which were unrelated to study medication. Three events were moderate in severity, and four events were severe in severity. Five subjects who received THC experienced the nonfatal SAEs of metastases to brain, gastric ulcer hemorrhage, syncope, bronchopneumonia, hyperglycemia, confusion, oral candidiasis, somnolence, tremor, and disorientation. All events were unrelated to study medication, with the exception of a single episode of syncope, which was probably related to THC. Two events were moderate in severity, and eight events were severe in severity. No patients from the placebo group reported a nonfatal SAE.

### Discussion

Unrelieved cancer pain can result in significant distress and disability.<sup>1,39</sup> The results of this study show that the THC:CBD extract is an efficacious adjunctive treatment for

Table 4  
Most Common Treatment-Related Adverse  
Events (Reported by Three or More Patients)

| Description of Event | THC:CBD, n (%) | THC extract, n (%) | Placebo, n (%) |
|----------------------|----------------|--------------------|----------------|
| Somnolence           | 8 (13)         | 8 (14)             | 6 (10)         |
| Dizziness            | 7 (12)         | 7 (12)             | 3 (5)          |
| Confusion            | 4 (7)          | 1 (2)              | 1 (2)          |
| Nausea               | 6 (10)         | 4 (7)              | 4 (7)          |
| Vomiting             | 3 (5)          | 4 (7)              | 2 (3)          |
| Raised gamma GT      | 2 (3)          | 5 (9)              | 1 (2)          |
| Hypercalcemia        | 0              | 0                  | 3 (5)          |
| Hypotension          | 3 (5)          | 0                  | 0              |

GT = gamma glutamyl transferase.

cancer-related pain in patients who are not achieving an adequate analgesic response to opioids.

This study involved patients with advanced cancer, who had a mean disease duration of more than three years and moderate to severe levels of pain at entry (>4 on an NRS pain scale), despite ongoing opioid treatment. After two weeks of receiving study medication adjunctive to all other treatments, the THC:CBD extract group showed a statistically significant reduction in pain severity when compared with placebo, with a reduction in mean pain NRS scores from baseline of 1.37 points (22.6%). The pain NRS data were not normally distributed; hence, parametric and non-parametric analyses were conducted. This had no influence on the significance of the results. The heterogeneity in the distribution of the pain scores (many large negative and large positive results), combined with consensus-based recommendations,<sup>32</sup> highlight the importance of the responder analysis. These recommendations are primarily based on the results of an analysis of relationships between changes in pain intensity and patient reports of overall improvement in 10 clinical trials of chronic pain, with patients of diverse diagnoses, in which a clinically relevant response was defined as a reduction of pain of at least 30% from baseline to end of study.

In this current study population, 43% of patients taking the THC:CBD extract achieved a 30% or greater improvement in their pain score (equated to a mean improvement of 2.71 boxes), approximately twice the number of patients who achieved this response in the THC and placebo groups. The results of the responder analysis and the mean change

from baseline must be interpreted remembering that the study medications were adjunctive to existing treatments, including strong opioids, for the duration of the trial. Larger treatment differences from placebo may be noted in a study of longer duration, as evident in other conditions.<sup>23,24</sup>

At baseline, the mean daily use of opioid background medication was relatively high (271 mg of oral morphine equivalents). The change in number of daily doses of breakthrough medication between baseline and end of study showed a slight trend toward reduction and no relevant differences between treatment groups. Only a small number of patients recorded taking strong opioid breakthrough medication in their daily diaries during the baseline period or last three days on treatment. Of these, most showed consistent dosing patterns; the changes that did occur showed a trend toward a decrease in the number of doses taken in the THC:CBD group and an increase in the placebo group. There was a large range in the dose of background oral morphine equivalent treatment. These findings may be a reflection of different treatment models used in the participating countries and illustrates the need to include a more specific eligibility criteria of minimum opioid treatment in future studies. Less variation in the existing treatment regimens would enhance the interpretation of the efficacy result but would make recruitment to the study more challenging.

No statistically significant differences in patient-assessed sleep quality or nausea NRS scores or investigator-assessed pain control assessment were noted between the study medications and placebo. There was a significant improvement in the BPI-SF total score for THC but not for THC:CBD. Studies of longer duration in other indications have regularly shown that the quality of sleep in the THC:CBD group needs to be improved.<sup>26,27,33,40</sup> The differences between treatment groups in the memory, concentration, and appetite NRS diary scores are partly attributable to an apparent improvement in the placebo group.

The QLQ-C30 showed few differences between study medications and placebo. Considering the follow-up duration and the patient population, this is unsurprising. There were

marginal improvements in QLQ-C30 pain scores but significantly reduced cognitive function scores with the THC:CBD and THC groups compared with those of the placebo group. The statistically significant worsening in QLQ-C30 nausea and vomiting score seen with the THC:CBD extract compared with placebo was not seen in the diary scores for nausea and is confounded by a median change of 0 between the groups, making interpretation of this result difficult. Similarly, the changes in appetite reported in the patient diaries were not seen in the QLQ-C30.

The few statistically significant results of the secondary endpoints should be interpreted with caution because of the multiple analyses performed on the questionnaire and the overlap in content between some of the NRS scales and questionnaire items. However, there is a consistent impairment of cognitive function reported by patients in this study. Although the clinical significance of this finding is unclear, it warrants further careful assessment in long-term studies. It is accepted that there will be limitations and potential inaccuracies of patient-completed diary data, and future studies will look to refine this method of data completion.

The AEs seen in this study were similar to those seen in other clinical trials<sup>26,27,33–38</sup> Of the AEs leading to permanent cessation of study medication (17%, 12% and 3%, respectively, for THC:CBD extract, THC extract, and placebo), approximately half were considered to be related to study treatment. None of the 33 reported SAEs raised concerns regarding treatment safety. The incidence of death was comparable among treatment groups, and there were no treatment-related deaths. Despite some uncertainty in the total morphine equivalent dose received by patients, the safety profile adds evidence that this was a population with advanced disease; 13% of patients died during the study because of their underlying disease.

The THC:CBD and the THC medications were well tolerated. Patients were fully titrated at one week and maintained stable dosing throughout the treatment period, that is, there was no observed tendency to increase dose with time. This corresponded to a reduction in pain NRS score over the same period. The clinical response to pain with THC:CBD

extract oromucosal spray has not demonstrated tolerance in several clinical trials of longer duration.<sup>26,27,33–38</sup>

There is evidence of synergy between THC and morphine in pain, and THC may modulate endogenous opioid tone.<sup>41</sup> However, in this study, the THC:CBD combination showed a more promising efficacy profile than the THC extract alone. This finding is supported by evidence of additional synergy between THC and CBD. CBD may enhance the analgesic potential of THC by means of potent inverse agonism at CB<sub>2</sub> receptors,<sup>14</sup> which may produce anti-inflammatory effects, along with its ability to inhibit immune cell migration.<sup>42</sup> Additionally, CBD may modulate the potential unwanted effects of THC by means of antagonism at CB<sub>1</sub> receptors,<sup>39</sup> which potentially would provide a better safety profile for the THC:CBD medication in chronic use.

In conclusion, THC:CBD extract, a nonopioid analgesic, endocannabinoid system modulator, has been shown to be a useful adjunctive treatment for relief of pain in patients with advanced cancer who experience inadequate analgesia despite chronic opioid therapy. The reductions in pain scores were neither because of a change in opioid background medications nor because of an increase in use of breakthrough medication. Therefore, we can conclude that the observed reduction in pain scores is attributable to the positive analgesic effects of THC:CBD extract. These results are very encouraging and merit further study.

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